EPOC will create novel ways to Conquer and Cure Cancer

EPOC Researchers Catalog

Fiscal Year 2019
Introduction

In 2005, the National Cancer Center Japan (NCC) opened the “Research Center for Innovative Oncology” (RCIO) in the National Cancer Center Hospital East (NCCH) at the Kashiwa Campus to unite doctors and researchers in the research and development of drugs and medical devices. In 2015, RCIO was integrated with the “Exploratory Oncology Research & Clinical Trial Center” (EPOC), which was founded in 2012, and RCIO and EPOC were combined into a new organization, retaining the name of “Exploratory Oncology Research & Clinical Trial Center” (NCC-EPOC). This integration has enabled drug discovery seed research, biomarker discovery, and diagnostics and laboratory test development in collaboration with the National Cancer Center Research Institute (NCCRI), and provided seamless transitions to clinical studies conducted by the NCCH and NCCH via early phase clinical development and research activities in the NCC and NCCH. In addition to the intramural collaboration with NCC institutions, NCC-EPOC is collaborating with a wide variety of organizations and businesses domestically and internationally in various fields from academic institutions to drug makers, diagnostic and medical device developers and regulatory authorities including the Ministry of Health, Labour and Welfare and Pharmaceuticals and Medical Devices Agency (PMDA). Therefore, NCC-EPOC serves as the driving force for the development of new drugs and medical devices in Japan.

We are actively involved in the provision of research funds and consultation services for promising research idea, concept and primitive materials in the NCC and in the introduction of the cultivated idea, concept and primitive materials to Japanese and overseas academic institutions and companies. This brochure describes the studies undertaken by researchers at the Kashiwa Campus in the NCC-EPOC, with a focus on potential drug or medical device candidates that are of interest to Japanese and overseas academic institutions, various pharmaceutical companies and medical device developers, and describes the platforms applicable in research and development. The potential drug or medical device candidates that the NCC-EPOC researchers can provide include peptide vaccine treatment, alpha ray treatment, cancer stromal cell research, and delirium and dementia studies, covering a wide range of research fields. Joint research and development with the NCC-EPOC allows you to develop the research idea and concept into drugs or medical devices that can be applied in actual medical practice in a seamless manner. We would like to work together with you to promote the development of novel medicines for global cancer care.

Dr. Atsushi Ochiai
Director
Exploratory Oncology Research & Clinical Trial Center, National Cancer Center Japan
Overcoming Resistance to Cancer Therapy

Understanding of mechanisms of resistance using human cancer specimens

- Elucidation of resistant mechanisms to EGFR-TKI using human cancer specimens
- Development of novel cancer therapies targeting the Wnt/β-catenin pathway
- Development of novel cancer therapies targeting chromosome instability

Research background

The Division of Translational Genomics (Kashiwa) focuses on translational research (TR) and promotes the integration of basic studies and clinical observations. We previously identified the T790M mutation in the EGFR gene using human lung cancer tissues that showed resistance to first and second generation EGFR inhibitors, which led to the development of third-generation EGFR inhibitors. However, resistance to third-generation EGFR inhibitors has already been reported, which may be caused by gene alterations in the EGFR gene and/or other signaling pathways. In addition, tumors which show chromosome instability are refractory to PD-1 antibodies and other cancer therapies; thus, it is imperative to discover potential drug targets involved in chromosome instability.

Research activities

Based on our previous experiences using cancer specimens, we have developed research infrastructure and resources, such as single-cell analyses and PDX models from patients with lung cancer, to study resistance to all EGFR inhibitors. We have discovered that the Wnt/β-catenin pathway may be involved in the pathogenesis of lung cancer by analyzing human lung cancer tissues and currently try to identify novel target molecules for new cancer therapeutics. We are also interested in the mechanisms of intracellular stress caused by chromosome instability. We use cancer cell line models to discover novel treatment options.

Potential research assets

- Human lung cancer cell lines resistant to one- to third-generation EGFR inhibitors
- Multi-omics data obtained from cell line models including single-cell analysis
- PDX models established from pre- and post-treatment (therapeutics and types of cancer are negotiable)

Future research prospectives

We will continue to analyze multiomics data on human cancer specimens (such as genomes, epigenomes, transcriptomes, and metabolomes) to investigate genetic abnormalities, tumor-specific activation pathways, and mechanisms of resistance (i.e. EGFR inhibitors) for the development of novel cancer therapeutics.
Development of New Patient Stratification Techniques and Drugs

Establishment of analysis techniques for immune cells that reflect the tumor microenvironment

- Techniques for examining immune cells in the tumor microenvironment
- Identification of patient stratification markers based on the characteristics of various types of immune cells
- Provision of analysis techniques for immune cells (particularly immunosuppressive cells)

Research background

As genetic analysis becomes a common strategy, personalized medicine based on genetic analysis data on cancer cells is now being applied into the clinic. At present, therapeutic agents, molecular-targeted reagents are prescribed to patients on the basis of the genetic analysis results of cancer cells, including EGFR mutations, ALK fusion gene expression; however, data from cancer cell genetic analysis are insufficient to determine the appropriate immunotherapy for many patients. Thus, the Division of Cancer Immunology focused not only on cancer cells but also on tumor-infiltrating immune cells for the optimal application of cancer immunotherapy based on the combination of genetic and immune analyses. We apply immune cell analysis techniques to identify new patient stratification markers and will contribute to the development of personalized medicine via new drug development activities.

Research characteristics

It was difficult to accurately understand the condition of immune cells in the tumor microenvironment because of the difficulty to collect sufficient amounts of samples from tumor tissues. The utilization of new techniques that we developed has enabled the extraction of immune cells while maintaining the phenotypes and functions of immune cells in the tumor microenvironment. Furthermore, using this technique, we have identified new patient stratification markers on the basis of the expression of immune cell molecules and have prospectively evaluated their clinical benefits. We mainly focus on clarifying the immunosuppressive mechanisms of regulatory T cells (such as CD8 positive T cell anergy) and are committed to the development of new cancer immunotherapy.

Potential research technical cooperation

- Techniques for extracting the immune cells reflecting the tumor microenvironment
- Analysis of patient stratification markers based on the analysis of immune responses in the tumor microenvironment
- Provision of various immunoassay techniques by focusing on regulatory T cells for drug discovery research

Future research prospects

The current cancer immunotherapy is not effective for all cancer patients since cancer cells employ various immunoselection strategies characterized by the loss of highly immunogenic antigens and by the establishment of immune suppressive mechanisms. We will integrate the genetic analyses about cancer cells and immune cells and their positional information inside the tumor and clarify the roles of immune cells in the entire tumor microenvironment to develop effective treatment options.

Immuno-genome assay

Sufficient amount of cells can be prepared for Immuno-genome assay

Frozen sample

Fresh sample

CD3+ cells

Frozen

536

54076

Fresh

\( p = 0.024 \)

Frozen

Fresh

Gastric cancer

Biopsy

Tumor size (mL)

Tumor-infiltrating cells

Baseline

1.0

1.5

2.0

2.5

3.0

3.5

# of biopsy

\( 0.1 \)

\( 1.0 \)

\( 10 \)

\( 50 \)

\( 100 \)
T Cell Therapy Targeting Unique Cancer Antigens
GPC3-, HSP105-, and neoantigen-targeted T cell therapy

▶ GPC3-targeted TCR-T/CAR-T cell therapy and HSP105-targeted TCR-T cell therapy
▶ Personalized T cell therapy by restored tumor-reactive, tumor-infiltrating lymphocytes
▶ Use of blood for the risk diagnosis of cancer development and cancer prophylaxis by vaccination

Research background

Many genetic mutations are accumulated in cancer cells, thus leading to the emergence of cancer antigens indicative of cancer cells. Cancer antigens are usually not present in the body and are recognized as foreign by lymphocytes (particularly CD8 positive T cells). Once the cancer antigens are recognized as foreign, they are attacked by CD8 positive T cells and are eliminated from the body. We identified GPC3 and HSP105, which are known as cancer antigens, and are conducting research for a wide range of clinical applications, including cancer prevention and treatment. A clinical study of GPC3 peptide vaccines has produced outstanding results (i.e., postoperative recurrence was not observed and no treatment was needed). A deficiency (impaired function) of tumor-infiltrating lymphocytes (TILs) has been reported to reduce the efficacy of anti-PD-1 antibodies and cell-based therapy. We are undertaking a “TIL rejuvenation study” to cure the deficiency of tumor-reactive TILs by aiming at the realization of TIL therapy in which the restored TILs are returned to the body. Furthermore, we are also studying the practical applications of genetically modified T cell therapy, such as GPC3-targeted CAR-T and HSP105-targeted TCR-T, for patients who failed to respond to the TIL therapy.

Research characteristics

The Division of Cancer Immunotherapy explores the application of unique cancer antigens for prevention and treatment. When GPC3 peptide vaccines were administered to five children with refractory hepatoblastoma who had multiple episodes of relapse and surgery, the cancer did not recur within 4 years, and no treatment was needed. A deficiency (impaired function) of tumor-infiltrating lymphocytes (TILs) has been reported to reduce the efficacy of anti-PD-1 antibodies and cell-based therapy. We are undertaking a “TIL rejuvenation study” to cure the deficiency of tumor-reactive TILs by aiming at the realization of TIL therapy in which the restored TILs are returned to the body. Furthermore, we are also studying the practical applications of genetically modified T cell therapy, such as GPC3-targeted CAR-T and HSP105-targeted TCR-T, for patients who failed to respond to the TIL therapy.

Potential research technical cooperation

◆ GPC3 and HSP105 peptide vaccines and TCR-T/CAR-T cell therapy
◆ Personalized T cell therapy for clinical application
◆ Use of blood for the risk diagnosis of cancer development and cancer prevention by vaccination

Future research prospects

We aim to achieve the practical use of TCR-T/CAR-T cell therapy by targeting unique cancer antigens, such as GPC3 and HSP105, and by using personalized tumor-reactive TIL/TCR-T cell therapy. We are also committed to the development of blood-based diagnostic methods for cancer development risk and vaccines for cancer prevention.
Provision of Elderly Oriented Care

Training programs for providing appropriate medical care to the elderly

- Training programs for educating staff on delirium and spreading the knowledge of delirium
- Provision of cancer treatment support programs for dementia patients
- Pathophysiological studies on chemobrain

Research background

Psycho-oncology is a composite discipline that seeks to clarify the anthropological side of cancer by applying knowledge in fields such as psychiatry, oncology, psychology, sociology, and ethics. As a society ages, the number of dementia patients undergoing cancer treatment increases. The development of delirium (cognitive impairment) during cancer treatment may also increase the risk of falling and interfere with daily activities after discharge. The Division of Psycho-Oncology is attempting to develop a system that can be implemented effectively at medical institutions in Japan for ensuring that elderly patients safely receive treatment and have a high quality of life during the treatment period.

Research characteristics

As the only research division in Japan specializing in mental support for cancer patients, the Division of Psycho-Oncology works in coordination with the Department of Psycho-Oncology at the Hospital East on initiatives for the development and provision of optimal support methods for patients, parents, bereaved family members, and medical staff. We have developed training programs to support healthcare professionals who respond to delirium. We have also created programs for supporting healthcare professionals to ensure that dementia patients can receive cancer treatment in a proper and smooth manner. We are conducting a study to reveal the pathophysiology of delirium and chemobrain (a temporary decrease in cognitive function, such as memory and concentration, during and after anticancer treatment).

Potential research technical cooperation

- Delirium education and training programs
- Cancer treatment support programs for dementia patients
- Pathophysiological findings of chemobrain

Future research prospects

Given that studies on the pathophysiology of delirium are lacking, we want to clarify the mechanisms of delirium and develop an automatic sensor system for delirium induced by cancer treatment. Once chemobrain develops, patients will suffer from poor concentration and severe forgetfulness, which will greatly affect their social life in the workplace or at home. We will make an effort to develop therapeutic agents for chemobrain and encourage cancer patients to return to society early.

Development of AI support system for dementia care

1. Constructing a registry of dementia in acute care setting
2. Implementation of deep learning and cross-validation using evaluation data
3. Validation of the AI support system (reflecting preferences of the persons with dementia and their families)
Application of Fibroblasts to Drug Development
Clarification of drug resistance caused by cancer-associated fibroblasts

- Establishment of primary cultured fibroblasts derived from the cancerous and noncancerous tissue samples of the same patients
- Establishment of primary cultured fibroblasts before and after drug treatment
- Creation of cancer organoids mixed with fibroblasts and cancer cell lines

Research background
The solid tumor microenvironment has a complicated structure composed of various cells, including cancer cells, fibroblasts, and immune cells. Recent studies show that intratumoral fibroblasts are functionally and phenotypically heterogeneous and affect the drug sensitivity of cancer cells via the interaction with these cells. The Division of Pathology, in cooperation with the Department of Pathology and Clinical Laboratories at the Hospital East, has established fibroblasts derived from human cancer tissues to clarify new mechanisms of cancer progression and develop new therapeutic agents.

Research characteristics
The Division of Pathology has built a technology for establishing the primary cultured cells of cancer-associated fibroblasts (CAF) from tumors, such as human lung and gastric cancers. We have also established normal fibroblasts (Non-CAF) simultaneously from noncancerous tissue samples from the same patients and identified the biological characteristics of CAFs by comparing CAFs and N-CAF with clinical information in mind. We also started drug sensitivity evaluation after establishing a system for cancer organoids mixed with CAFs and cancer cell lines. We have established CAFs from human cancer tissues that are not treated with drugs, and we recently succeeded in establishing the CAFs from those treated with drugs. We will attempt to clarify the causes of CAF-induced drug resistance.

Potential research technical cooperation
◆ CAFs and N-CAFs from the same patients
◆ System for cancer organoids mixed with CAFs and cancer cell lines
◆ Establishment of CAFs before and after drug treatment

Future research prospects
We will try to clarify the roles of CAFs in the tumor microenvironment before and after drug treatment. Focusing on the interaction between drug-exposed CAFs and drug-exposed cancer cells, we will develop a novel therapeutic strategy.

Organoids using tissue-derived CAFs and cancer cells
(Lung Cancer, 2019; 100-107)

Local invasion evaluation system using tissue-derived CAFs and cancer cells
(Int. J Cancer, 2015;784-96)
(Adv Drug Deliv Rev. 2016;186-196)
Novel Antibody Therapeutics with Competitive Advantages

Demonstration of tumor regression in PDX model where standard treatment does not work

- Identification of two different unique monoclonal antibodies (mAb)
- Novel mAb effective in the PDX models of EGFR antibody-resistant colorectal cancer (CRC)
- Antibody-modified platform technology using anticancer agents or radioisotopes

Research background

The Enhanced Permeability and Retention (EPR) effect, in which macromolecular substances are retained at the tumor site for a long time, has been proven in animal experiments. However, unlike animal models, the human cancer tissue has a complicated structure and is composed of not only cancer cells but also stromal tissues. Therefore, the clinical effectiveness of the EPR effect has not been demonstrated in human cancer tissues. The Division of Developmental Therapeutics has acquired mAbs that recognize a new molecule, TMEM-180, which is found in 50% of colorectal cancer and 30% of ovarian and breast cancers. The administration of TMEM-180 mAb induced tumor regression in the CRC PDX refractory to EGFR mAbs. We have also acquired mAbs that specifically recognize the 3D structure of insoluble fibrin. We are actively engaged in developing a new drug by combining these antibodies with toxin or radioisotope At211 or Ac225 (alpha ray-emitting nuclide).

Research characteristics

- The Division of Developmental Therapeutics has successfully acquired unique antibodies that recognize a new molecule of colorectal cancer, namely, TMEM-180, which is found in 50% of colorectal cancer and 30% of ovarian and breast cancers. The administration of TMEM-180 mAb induced tumor regression in the CRC PDX refractory to EGFR mAbs. We have also acquired mAbs that specifically recognize the 3D structure of insoluble fibrin. We are actively engaged in developing a new drug by combining these antibodies with toxin or radioisotope At211 or Ac225 (alpha ray-emitting nuclide).

Potential research technical cooperation

- Production of master cell bank specifically recognizing TMEM-180 or insoluble fibrin
- ADC platform technology for combining toxin with antibodies
- Platform technology for combining alpha ray-emitting radioisotopes with antibodies

Future research prospects

We are going to work with companies on the practical use of TMEM-180 mAbs and produce its modified antibodies. We will strongly promote the TR study of our unique insoluble fibrin-specific antibodies to evaluate CAST therapy in actual medical practice and to provide new treatment options for stroma-rich intractable cancers.
Clinical Application of Alpha Ray-Emitting Radionuclide therapy

Establishment of alpha ray-emitting radionuclides therapy system for TR studies and clinical trials

▶ Non-clinical studies utilizing advanced facilities for alpha ray-emitting radionuclides
▶ TR studies with alpha ray-emitting radionuclides including the evaluation using human cancer tissues
▶ Development of imaging techniques for theranostics

Research background

Early cancer detection and the development of effective cancer treatment have improved the prognosis of cancer patients; however, no good treatment has been established for patients with some intractable cancers. The Division of Functional Imaging is developing various diagnostic imaging techniques (e.g., nuclear medicine tests, magnetic resonance imaging [MRI] tests, optical imaging tests) for the visualization of intractable cancer lesions and their characteristics to improve the prognosis of patients suffering from intractable cancers. Furthermore, we have applied these diagnostic techniques to novel treatment methods for intractable cancers (theranostics).

Research characteristics

The Division of Functional Imaging has established a technology for detecting microscopic pancreatic cancer in mice by using high-affinity RGD peptides combined with radionuclides. We are trying to put this technology to practical use as a diagnostic agent for pancreatic cancer to improve the prognosis of patients with pancreatic cancer. Furthermore, we have recently built research facilities where alpha ray-emitting radionuclides can be used in the Kashiwa Campus, thus enabling us to conduct TR for nuclear medicine therapy. We have newly built facilities for the GMP-compliant synthesis of investigative drugs and plan to conduct a new clinical trial including alpha ray-emitting radionuclides. We are also working on the development of unique theranostics based on the combined use of novel diagnostic imaging techniques (including 3D optical imaging using near-infrared lights with longer wavelength than 1,000 nm).

Potential research technical cooperation

▶ Provision of nonclinical research facilities where radionuclides can be used.
▶ TR utilizing radionuclides
▶ Development of theranostics using tomographic imaging of near-infrared lights with long wavelengths

Future research prospects

In Japan, there are small number of facilities where non-clinical studies and clinical trials using radionuclides can be seamlessly performed. The Division of Functional Imaging is well collaborating with the Hospital East to conduct TR studies using human cancer tissues and perform drug development researches. We are also actively engaged in the research and development of theranostics, which is a combination of diagnosis and treatment, for its clinical application.
Drug Discovery by Co-Clinical Trials

Assessment of compounds in PDX models and/or cancer organoids

- Investigative research pertaining to the usefulness of PDX models
- PDX models and/or cancer organoids using human cancer tissues
- Drug discovery by co-clinical trials

Research background

Although cancer cell lines and cell line-derived xenograft (CDX) models have been used for the development of anticancer drugs for a long period of time, there is a growing need for animal models that reflect individual patient conditions not only in Europe and the United States but also in Japan after the introduction of genomic medicine. The patient-derived xenograft (PDX) models, in which the patient-derived cancer tissues are transplanted to immunocompromised mice, allow researchers to conduct evaluations on the basis of the patients' genetic backgrounds, thus potentially leading to the selection of appropriate therapeutic agents and further research on study drug resistance. The Section of Experimental Animals is working together with J-PDX Project to develop an infrastructure for PDX models, system for cancer organoids (3D culture system), and co-clinical trials (concurrent clinical studies).

Research characteristics

The Section of Experimental Animals investigates the actual use, application, and trend of PDX models for drug discovery in Japan and overseas to analyze the issues and identify the points to consider. Our analysis revealed that one of the biggest issues was the establishment of PDX models that are capable of reproducing the human cancer microenvironment in the mouse body. To contribute to the promotion of drug development, we are working on the basic studies of PDX models using human cancer tissues and cancer organoids and on the standardization of quality control procedures for these parameters.

Potential research technical cooperation

◆ Provision of PDX models
◆ Provision of cancer organoids
◆ Drug development and research support using co-clinical trials

Future research prospects

We will make the best use of PDX models derived from human cancer tissues, genetically modified animals, and cancer organoids and will establish a co-clinical trial system to reduce the time and cost required for clinical trials and deliver drugs to patients as soon as possible.

Non clinical drug development

in vitro
- 2D culture
- 3D culture
- Organoids

in vivo
- Mouse cell-line derived allograft model
- Genetically engineered mouse model (GEMM)
- Human cell-line derived xenograft (CDX) model
- PDX (Patient-derived xenograft) model

2D culture
Easy/No need for DDS technology

3D culture
Need DDS technology for delivery to the center of the cancer cells

Cancer cells affected by cancer stroma cells

Clinical trial
Entry to the trials
1st line therapy
2nd line therapy
3rd line therapy
Progression
Progression
Progression

PDX
Humanized PDX

Non-clinical trial: PDO (patient-derived organoid) or PDX (patient-derived xenograft)
Basic information

Foundation September 1st, 2012

Director Dr. Atsushi Ochiai

History

October 2005 Research Center for Innovative Oncology was established in National Cancer Center Hospital East.

April 2008 Office of Clinical Research was opened at the center. A support system for investigator-initiated clinical studies was organized.

July 2011 National Cancer Center was selected as a center of the “Project for Organization of Early/Exploratory Clinical Trial Centers,” and Phase 1 Center was established as a center of new cancer drug development in close cooperation between National Cancer Center Hospital East/Research Center for Innovative Oncology and Center Hospital/Research Institute. Several development studies were initiated, including sponsor- and investigator-initiated first-in-human studies.

July 2012 Office of Translational Research was opened. A full-scale support system for translational research (TR) was established.

September 2012 Exploratory Oncology Research & Clinical Trial Center (EPOC) was established.

April 2015 Research Center for Innovative Oncology was integrated into EPOC. Atsushi Otsu (current Director, National Cancer Center Hospital East) was appointed as the Director of this center.

May 2016 EPOC reorganization was performed to focus on nonclinical studies aiming at demonstrating concepts of drug discovery and early and exploratory clinical TR studies. Atsushi Ochiai was appointed as the Director of this center.

May 2019 Memorandums on research cooperation were concluded with Shonan Health Innovation Park (iPark) and Cancer Center at Beth Israel Deaconess Medical Center, Boston, the U.S.A., respectively.

June 2019 A master agreement was concluded with Miraca Holdings Inc. and Mitsui Fudosan Co., Ltd., for cooperation and collaboration for development of next-generation medical techniques and healthcare services.

Activities

We consistently support new idea, concept and primitive materials designed to become approved as cancer drugs or medical devices with an aim of “Conquer and Cure Cancer (3C).”

◆ Establishment of a system to promote cross-sectional TR studies among National Cancer Center Hospital East, Central Hospital and Research Institute
◆ Promotion of TR studies using quality-controlled clinical samples associated with clinical information
◆ Elucidation of the fundamental mechanism of intractable or refractory cancer
◆ Exploration of therapeutic targets and development of medical devices for supportive therapy
◆ Drafting clinical development plans for drug or medical device candidates derived from within and without National Cancer Center Japan
◆ Acceleration of an effective industry-academia cooperation
◆ Education of global human resources involved in medical development

Inquiry on collaborative research

If you have any requests or questions, please feel free to contact Seeds Development Support Section.

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